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EXAMINER	
RAMACHANDRAN, UMAMAHESWARI	
ART UNIT	PAPER NUMBER
1617	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/734,640	LIGNIERES ET AL.	
	Examiner	Art Unit	
	UMAMAHESWARI RAMACHANDRAN	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 February 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4 and 6-14* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4, 6-14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The examiner notes the receipt of the amendments and remarks received in the office on 2/21/2008. The terminal disclaimer filed on 2/21/2008 disclaiming the terminal part of the term of any patent granted on U.S. Patent Application 10/734,640 which would extend beyond the full statutory term, as shortened by any terminal disclaimer, of any patent granted on U.S. Patent Application 10/734,638 has been reviewed and accepted. Claim 5 is cancelled. Claims 1-4, 6-14 are pending and are being examined on the merits herein.

Response to Remarks

Applicants' arguments regarding the rejection of claims 1-3, 6-8, 10, 11-14 under 35 U.S.C. 103(a) as being unpatentable over Jarvis (Current Therapy in Endocrinology and Metabolism, 280-284) in view of Pujol et al. (Cancer Chemother Pharmacol, 36, 493-498, 1995) and further in view of in view of Fentiman et al. (Br. J. Surg, 75, 845-846, 1988) and rejection of claims 1-3, 6-8, 10, 11-14 under 35 U.S.C. 103(a) as being unpatentable over Jarvis et al. ("Hormonal Therapy of Benign Breast Disease," Senologie et Pathologie Mammaire.4eme Congres International, Paris 1-4 September 1986, pp. 128-132) in view of Pujol et al. (Cancer Chemother Pharmacol, 36, 493-498, 1995) and further in view of in view of Fentiman et al. (Br. J. Surg, 75, 845-846, 1988) and rejection of claims 1-3, 6-8, 10,11-14 under 35 U.S.C. 103(a) as being unpatentable over Pujol et al. (Cancer Chemother Pharmacol, 36, 493-498, 1995) in view of Fentiman et al. (Br. J. Surg, 75, 845-846, 1988) and rejection of claim 9 under 35 U.S.C. 103(a) as being unpatentable over Pujol et al. (Cancer Chemother Pharmacol, 36, 493-498,

1995) in view of Fentiman et al. (Br. J. Surg, 75, 845-846, 1988) as applied to claims 1-3, 6-8, 10, 11-14 above and further in view of Kochinke et al. (U.S. 5,613,958) and rejection of claim 4 under 35 U.S.C. 103(a) as being unpatentable over Pujol et al. (Cancer Chemother Pharmacol, 36, 493-498, 1995) in view of Fentiman et al. (Br. J. Surg, 75, 845-846, 1988) as applied to claims 1-3, 6-8, 10, 11-14 above and further in view of Malet et al (Cancer Research, 48, 7193-7199, 1988) have been fully considered and found not persuasive. The rejections are maintained and are given below for Applicants' convenience. The action is made Final.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-3, 6-8, 10, 11-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jarvis (Current Therapy in Endocrinology and Metabolism, 280-284)

in view of Pujol et al. (Cancer Chemother Pharmacol, 36, 493-498, 1995) and further in view of in view of Fentiman et al. (Br. J. Surg, 75, 845-846, 1988).

Jarvis teach studies have been performed to determine if 4-hydroxy tamoxifen, a very active metabolite of tamoxifen that has an affinity for the estrogen receptor 100 times greater than that of tamoxifen, can be used percutaneously to avoid the systemic effects of the oral administration of tamoxifen in benign breast disease. The reference further teaches the results from those studies that 4-hydroxy tamoxifen when topically applied in alcoholic solution over the human breast is absorbed through the skin and is retained. The reference teaches that tamoxifen has been proposed for the treatment of benign breast disease (one of the symptoms being breast pain (mastodynia or mastalgia) but due to drawback of its use in premenopausal women leading to an increase in gonadotropin secretion studies were performed with 4-hydroxy tamoxifen (p 281, col. 1, col. 2, Antiestrogens).

The reference does not teach the amount of 4-hydroxy tamoxifen in the percutaneous administration.

Pujol et al. teaches a percutaneous administration of 0.5 mg, 1.0 mg, 2.0 mg of 4-hydroxy tamoxifen in a hydroalcoholic gel to breast areas for the treatment of breast cancer (see Abstract, p 494, study design).

Jarvis and Pujol et al. do not teach mastalgia to be cyclical.

Fentiman teaches a method of treatment of mastalgia comprising oral administration of 10 or 20 mg of tamoxifen to patients with either cyclical or non-cyclical breast pain (see Abstract, p 845, col. 2, lines 10-12).

It would have been obvious to one of ordinary skill in the art at the time of the invention to administer 4-hydroxy tamoxifen at a dose of at least 1.5 mg/day or the dosages claimed in the instant invention. One of ordinary skill in the art would have been motivated to administer such claimed amounts of 4-hydroxy tamoxifen in the treatment of mastalgia because of expectation of success as Pujol et al. clearly teaches percutaneous administration of 4-OH-tamoxifen (0.5 mg and 1.0 mg/breast) to patients. The examiner respectfully points out the following from MPEP 2144.05: "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." I*n re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955); see also Peterson, 315 F.3d at 1330, 65 USPQ2d at 1382 ("The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages."); *In re Hoeschele*, 406 F.2d 1403, 160 USPQ 809 (CCPA 1969); Merck & Co. Inc. v. Biocraft Laboratories Inc., 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), cert. denied, 493 U.S. 975 (1989); *In re Kulling*, 897 F.2d 1147, 14 USPQ2d 1056 (Fed.Cir. 1990); and *In re Geisler*, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997). It would have been obvious to one of ordinary skill in the art to use 4-hydroxy tamoxifen in a method of treatment of cyclical mastalgia. One of ordinary skill in the art would have been motivated to use 4-hydroxy tamoxifen in a method of treatment of cyclical mastalgia because of the teachings of Fentiman and Jarvis. Jarvis teach the use of 4-hydroxy tamoxifen in benign breast disease (mastalgia, which includes both cyclical and non-cyclical) and the advantages

of using 4-hydroxy tamoxifen over tamoxifen and Fentiman teaches the use of tamoxifen in the treatment of both cyclical and non-cyclical breast pain. It would have been obvious to one of ordinary skill in the art to use 4-hydroxy tamoxifen for tamoxifen in the treatment of cyclical breast pain as Jarvis teaches the drawbacks of using tamoxifen and the advantages of 4-OH tamoxifen and it is well known in the art that 4-OH tamoxifen is an active metabolite of tamoxifen.

Claims 1-3, 6-8, 10, 11-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jarvis et al. ("Hormonal Therapy of Benign Breast Disease," Senologie et Pathologie Mammaire.4eme Congres International, Paris 1-4 September 1986, pp. 128-132) in view of Pujol et al. (Cancer Chemother Pharmacol, 36, 493-498, 1995) and further in view of in view of Fentiman et al. (Br. J. Surg, 75, 845-846, 1988).

Jarvis et al. teach studies have been performed to determine if 4-hydroxy tamoxifen, a very active metabolite of tamoxifen that has an affinity for the estrogen receptor 100 times greater than that of tamoxifen, can be used percutaneously to avoid the systemic effects of the oral administration of tamoxifen in benign breast disease. The reference further teaches the results from those studies that 4-hydroxy tamoxifen when topically applied in alcoholic solution over the human breast is absorbed through the skin and is retained. The reference teaches that tamoxifen has been proposed for the treatment of benign breast disease (one of the symptoms being breast pain (mastodynia or mastalgia) but due to drawback of its use in premenopausal women leading to an increase in gonadotropin secretion studies were performed with 4-hydroxy tamoxifen (p 129, 130, Therapeutic Alternatives, Antiestrogens).

The reference does not teach the amount of 4-hydroxy tamoxifen in the percutaneous administration.

Pujol et al. teaches a percutaneous administration of 0.5 mg, 1.0 mg, 2.0 mg of 4-hydroxy tamoxifen in a hydroalcoholic gel to breast areas for the treatment of breast cancer (see Abstract, p 494, study design).

Jarvis and Pujol et al. do not teach mastalgia to be cyclical.

Fentiman teaches a method of treatment of mastalgia comprising oral administration of 10 or 20 mg of tamoxifen to patients with either cyclical or non-cyclical breast pain (see Abstract, p 845, col. 2, lines 10-12).

It would have been obvious to one of ordinary skill in the art at the time of the invention to administer 4-hydroxy tamoxifen at a dose of at least 1.5 mg/day or the dosages claimed in the instant invention. One of ordinary skill in the art would have been motivated to administer such claimed amounts of 4-hydroxy tamoxifen in the treatment of mastalgia because of expectation of success as Pujol et al. clearly teaches percutaneous administration of 4-OH-tamoxifen (0.5 mg and 1.0 mg/breast) to patients. The examiner respectfully points out the following from MPEP 2144.05: "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." I*n re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955); see also Peterson, 315 F.3d at 1330, 65 USPQ2d at 1382 ("The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages."); *In re Hoeschele*,

406 F.2d 1403, 160 USPQ 809 (CCPA 1969); Merck & Co. Inc. v. Biocraft Laboratories Inc., 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), cert. denied, 493 U.S. 975 (1989); *In re Kulling*, 897 F.2d 1147, 14 USPQ2d 1056 (Fed.Cir. 1990); and *In re Geisler*, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997). It would have been obvious to one of ordinary skill in the art to use 4-hydroxy tamoxifen in a method of treatment of cyclical mastalgia. One of ordinary skill in the art would have been motivated to use 4-hydroxy tamoxifen in a method of treatment of cyclical mastalgia because of the teachings of Fentiman and Jarvis. Jarvis teach the use of 4-hydroxy tamoxifen in benign breast disease (mastalgia, which includes both cyclical and non-cyclical) and the advantages of using 4-hydroxy tamoxifen over tamoxifen and Fentiman teaches the use of tamoxifen in the treatment of both cyclical and non-cyclical breast pain. It would have been obvious to one of ordinary skill in the art to use 4-hydroxy tamoxifen for tamoxifen in the treatment of cyclical breast pain as Jarvis teaches the drawbacks of using tamoxifen and the advantages of 4-OH tamoxifen and it is well known in the art that 4-OH tamoxifen is an active metabolite of tamoxifen.

Claims 1-3, 6-8, 10,11-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pujol et al. (Cancer Chemother Pharmacol, 36, 493-498, 1995) in view of Fentiman et al. (Br. J. Surg, 75, 845-846, 1988).

Pujol et al. teaches a percutaneous administration of 0.5 mg, 1.0 mg, 2.0 mg of 4-hydroxy tamoxifen in a hydroalcoholic gel to breast areas for the treatment of breast cancer (see Abstract, p 494, study design). The reference further teaches that 4-hydroxy tamoxifen is an active metabolite of tamoxifen (p 497, col. 1, line 18). Pujol et

al. do not explicitly teach 4-hydroxy tamoxifen to be a racemic mixture but it is obvious that the compound has both the cis and trans isomers.

The reference does not teach 4-hydroxy tamoxifen in the treatment of mastalgia.

Fentiman teaches a method of treatment of mastalgia comprising oral administration of 10 or 20 mg of tamoxifen to patients with either cyclical or non-cyclical breast pain (see Abstract, p 845, col. 2, lines 10-12).

It would have been obvious to one of ordinary skill in the art at the time of the invention to use 4-hydroxy tamoxifen in the treatment of mastalgia. The motivation to do so is provided by Pujol et al. The reference teaches that 4-OH-tamoxifen is an active metabolite of tamoxifen and has 100-1000 fold stronger affinity to estrogen receptors compared to tamoxifen and the reference further teaches 4-OH-tamoxifen to be one of the most potent anti-estrogens and the compound penetrates through the skin. The reference also teaches that 4-OH-tamoxifen gel administration is associated with low systemic effects yet induces moderate breast tissue concentration.

Fentiman et al. and Pujol et al. do not teach administration of 0.75mg/breast of 4-OH-tamoxifen or a dose of 1.5 mg/day to patients but Pujol teaches administration of 4-OH-tamoxifen (0.5 mg and 1.0 mg/breast) to patients.

The examiner respectfully points out the following from MPEP 2144.05: “[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.” I*n re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955); see also Peterson, 315 F.3d at 1330, 65 USPQ2d at 1382 (“The normal desire of scientists or artisans to improve upon what

is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages."); *In re Hoeschele*, 406 F.2d 1403, 160 USPQ 809 (CCPA 1969); Merck & Co. Inc. v. Biocraft Laboratories Inc., 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), cert. denied, 493 U.S. 975 (1989); *In re Kulling*, 897 F.2d 1147, 14 USPQ2d 1056 (Fed.Cir. 1990); and *In re Geisler*, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997).

Claim 9 is rejected under 35 U.S.C. 103(a) as being unpatentable over Pujol et al. (Cancer Chemother Pharmacol, 36, 493-498, 1995) in view of Fentiman et al. (Br. J. Surg, 75, 845-846, 1988) as applied to claims 1-3, 6-8, 10, 11-14 above and further in view of Kochinke et al. (U.S. 5,613,958).

The teachings of Pujol et al. (Cancer Chemother Pharmacol, 36, 493-498, 1995) in view of Fentiman et al. (Br. J. Surg, 75, 845-846, 1988) have been discussed in the 103(a) rejection set forth above.

Pujol et al. and Fentiman et al. do not teach the hydroalcoholic gel comprising ethanol, isopropyl myristate and hydroxypropyl cellulose.

Kochinke et al. teaches a transdermal drug delivery system comprising a drug, plasticizer-type enhancer such as isopropyl myristate, a solvent-type enhancer such as ethanol and a gelling agent such as hydroxypropyl cellulose (col. 9, lines 23-25, 47-59, col. 11, lines 6-25).

It would have been obvious to one of ordinary skill in the art to use a combination of isopropyl myristate, ethanol, and hydroxypropyl cellulose as a hydroalcoholic gel solution in the percutaneous delivery of 4-OH tamoxifen. The motivation to do so is

provided by Kochinke et al. The reference teaches that solvent-type enhancer such as ethanol provide higher flux rate, plasticizer-type enhancer such as isopropyl myristate is used in combination with a solvent-type enhancer to deliver drugs through stratum corneum at therapeutically effective levels and to eliminate the irritation that occurs when solvent-type enhancers are used alone at high concentrations. In addition the reference teaches that a gelling agent such as hydroxypropylcellulose is added to increase the viscosity and rheological characteristics of the drug and enhancers.

Claim 4 is rejected under 35 U.S.C. 103(a) as being unpatentable over Pujol et al. (Cancer Chemother Pharmacol, 36, 493-498, 1995) in view of Fentiman et al. (Br. J. Surg, 75, 845-846, 1988) as applied to claims 1-3, 6-8, 10, 11-14 above and further in view of Malet et al (Cancer Research, 48, 7193-7199, 1988).

The teachings of Fentiman et al. (Br. J. Surg, 75, 845-846, 1988) in view of Pujol et al. (Cancer Chemother Pharmacol, 36, 493-498, 1995) have been discussed in the 103(a) rejection set forth above.

Pujol et al. and Fentiman et al. do not teach percutaneous administration of trans 4-hydroxy tamoxifen in the treatment of mastalgia.

Malet teaches percutaneous administration of trans 4-hydroxy tamoxifen to human breast of patients (see Abstract). The reference further teaches that trans-4-hydroxy tamoxifen is a very active metabolite of tamoxifen.

It would have been obvious to one of ordinary skill in the art to use trans 4-hydroxy tamoxifen for the treatment of mastalgia. The motivation to do so is provided by Malet et al. The reference teaches that trans-4-hydroxy tamoxifen is a very active

metabolite of tamoxifen. The reference further teaches that cis-4-hydroxy tamoxifen exerts a potent estrogenic agonistic effect and a percutaneous administration of trans 4-hydroxy tamoxifen could produce a strong antiestrogenic effect at the molecular level.

Response to Arguments

Applicants' arguments regarding the rejections have been fully considered and found not to be persuasive. Applicants' argue that tamoxifen is not a prodrug of 4-OH tamoxifen and 4-OH tamoxifen is one of the three primary metabolites and not even a major metabolite. In response, it is not relevant that 4-OH tamoxifen is not a major metabolite but it is well known in the art that it is one of three primary metabolites. Applicants' further argue that someone skilled in the art would not expect 4-OHT to be biologically equivalent to tamoxifen based on the estrogen receptor binding affinity. It is known in the art that structurally related compounds might or might not have the same or equivalent biological activity because a small difference in the substitution can lead to different biological activities. Yet it would have been obvious to one of ordinary skill in the art at the time of the invention to administer 4-OHT in a method of treatment of mastalgia because 4-OHT is known to be an active metabolite and one of the primary metabolites of tamoxifen and further Jarvis's studies clearly suggests that the administration of 4-OH tamoxifen in the treatment of benign breast disease for tamoxifen to avoid the systemic effects of the oral administration of tamoxifen in benign breast disease. Applicants' argue that one of skilled in the art would not have administered 4-OHT for tamoxifen in the treatment of mastalgia because commercially available Z-isomer of tamoxifen yields only Z-isomer of 4-OHT that has only anti-

estrogenic activity. This is not persuasive because, the relative anti-estrogenic activity will depend on the amount of isomers present in the mixture and may not result in the estrogenic activity alone. In addition Jarvis et al. (U.S. 4,919,937) clearly teaches the benefits of 4-OH tamoxifen in benign cancer conditions and Jarvis (Current Therapy in Endocrinology and Metabolism, 280-284) teach mastodynia or mastalgia is associated with benign breast disease. Hence it would have been obvious to one of ordinary skill in the art at the time of the invention to have adminstered 4-OHT in a method of treatment of mastalgia. Applicants' argue that “different tamoxifen metabolites have different activities, tamoxifen has a number of biological activities and a number of biological active metabolites a priori, and predicting which specific activity and metabolite of tamoxifen might be useful for the treatment of breast condition is not an undertaking that can be carried out with any reasonable level of uncertainity”. In response this is not persuasive because there is prior art that teaches and suggests the administration of 4-OH tamoxifen in a method of treatment of benign breast diseases (Jarvis et al. (U.S. 4,919,937), Jarvis (Current Therapy in Endocrinology and Metabolism, 280-284), Jarvis et al. ("Hormonal Therapy of Benign Breast Disease," Senologie et Pathologie Mammaire.4eme Congres International, Paris 1-4 September 1986, pp. 128-132). As stated above mastalgia or mastodynia is associated with benign breast disease. In addition there are only three primary metabolites of tamoxifen and 4-OH tamoxifen being an active metabolite with an affinity for the estrogen receptor 100 times greater than that of tamoxifen, the level of uncertainity seems to be very low. It would have been clearly obvious from the prior literature to one of ordinary skill in the art that 4-OH

tamoxifen would be useful in a method of treatment of mastalgia. Also, as pointed out by the Applicants' that different metabolites have different biological activities one of skilled in the art would have been motivated to find out which metabolite of tamoxifen is responsible for the biological activity of tamoxifen. Applicants argue that other tamoxifen metabolites such as Droloxifene or another estrogen receptor modulator such as raloxifene has high level of unpredictability and hence the skilled artisian could not have reasonably predicted from the known estrogen binding activity of 4-OHT that 4-OHT could be used to treat mastalgia. This is not persuasive because if a metabolite of tamoxifen or an estrogen receptor modulator is less effective than tamoxifen does not mean that other metabolites cannot be used or will not be useful in a method of treatment of a disorder. In addition, one of ordinary skill in the art would have been motivated to test the other two primary metabolites after learning that droloxifene is found to be less effective than tamoxifen. Applicants' argue that 4-OHT is not the only active metabolite of tamoxifen for pharmacological activity and was not necessarily the most promising or viable choice for further study. This is not persuasive because it is irrelevant whether 4-OHT is not the only active metabolite of tamoxifen. The prior art teaches and suggests the administration of 4-OH tamoxifen in a method of treatment of benign breast diseases (Jarvis et al. (U.S. 4,919,937), Jarvis (Current Therapy in Endocrinology and Metabolism, 280-284), Jarvis et al. ("Hormonal Therapy of Benign Breast Disease," Senologie et Pathologie Mammaire.4eme Congres International, Paris 1-4 September 1986, pp. 128-132). Hence the prior art clearly suggests that 4-OHT is a promising choice in a method of treatment of benign breast diseases. Applicants' argue

that the prior art Pujol studies comes from post-menopausal breast cancer patients and the present invention relates to the treatment of mastalgia, a condition that arises in pre-menopausal patients. The arguments are not persuasive because, the primary reference Jarvis teach teaches and suggests the administration of 4-OH tamoxifen in a method of treatment of benign breast diseases The reference teaches that tamoxifen has been proposed for the treatment of benign breast disease (one of the symptoms being breast pain (mastodynia or mastalgia)). The secondary reference Pujol has been used to show the amount of 4-OHT that can be safely applied to breasts. It would have been obvious to one of ordinary skill in the art at the time of the invention that 4-OHT can be used in a method of treatment of benign breast diseases such as mastaglia from Jarvis's teachings. If the same drug as claimed is taught to be useful in a method of treatment of benign breast disease such as masgtalgia then the treatment applies to the same set of population. Applicants' argue that Pujol reference does not suggest that percutaneous 4-OHT can be successfully used in place of oral tamoxifen to breast cancer, let alone to treat mastalgia. In response, as stated earlier, Jarvis teach that 4-OHT can be used percutaneously to avoid the systemic effects of the oral administration of tamoxifen in benign breast disease. It would have been obvious to one of ordinary skill in the art at the time of the invention that 4-OHT can be used percutaneously in the treatment of benign breast disease. Applicants' argue that Jarvis's references are entirely speculative and not based on supporting clinical data. In response, Jarvis's teachings are used in the obviousness rejections. It would have been obvious from the teachings of Jarvis that benign breast diseases can be treated with the administration of

4-OHT. The studies clearly suggest and motivate a person of ordinary skill in the art to use 4-OHT in a method of treatment of benign breast disease, one of the symptoms being breast pain or mastalgia.

Conclusion

No claims are allowed.

The rejections are maintained and are given in the Office Action for Applicants' convenience. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Umamaheswari Ramachandran whose telephone number is 571-272-9926. The examiner can normally be reached on M-F 8:30 AM - 5:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on 571-272-0629. The

fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/SREENI PADMANABHAN/

Supervisory Patent Examiner, Art Unit 1617